REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1-6 and 21 are currently being amended. No new matter is being added. The amendments are supported by the specification, for example, on pages 2, 6 and 12. Upon entry of the amendments, claims 1-21 will be pending, with claims 7-20 withdrawn. Claims 1-6 and 21, accordingly, will be pending for examination on the merits.

I. Claim Objection

Claim 4 is objected for reciting the terms "HBV core (like) particles" and "HBV virus (like) particles." Office Action, pg. 4. The Examiner, however, provided suggestions for overcoming the objection. Applicants have amended the claims consistent with the suggestions and respectfully request withdrawal of the objection.

II. Claims 1-4 Have Utility

Claims 1-4 are rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Office Action, pg. 5. In line with the Examiner's suggestions, Applicants have amended the claims to include the term "isolated." Applicants, therefore, respectfully request withdrawal of the rejection.

III. Claims 1 and 3-6 Are Definite

Claims 1 and 3-6 are rejected under 35 U.S.C. § 112, second paragraph, because "the signal sequence" in claim 1 is allegedly unclear. Office Action, pp. 5-6. Without acquiescing to the merits of the rejection, Applicants have amended claim 1 to recite "comprising amino

acids at positions -29 to -11." Applicants, therefore, respectfully request withdrawal of the rejection.

IV. Claims 1 and 4 Are Adequately Described

Claims 1 and 4 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing the written description requirement. Office Action, pp. 6-7. Applicants respectfully traverse the rejection.

Regarding claim 1, the claim has been amended to recite "comprising amino acids at positions -29 to -11," which identifies the position of the claimed "signal sequence." This amendment is supported by the specification on page 2. The specification, therefore, provides adequate written description of the claimed "signal sequence."

Regarding claim 4, one skilled in the art would have know of the existence *per se* of hepatitis B virus-like particles lacking DNA, as evidenced by Sakamoto *et al.*, Laboratory Investigation, 48:678-682 (1983) ("Sakamoto"). Specifically, Sakamoto describes that, among Dane particles, there are empty particles containing no DNA. Specification, pg. 4. With this in mind, Applicants respectfully direct the Examiner's attention to Figure 3 of the application, which illustrates fractionation results of HBcrAg (the claimed "HBV core-like particle"), HBcAg, HBV-DNA, and HBsAg. See also, specification, pp. 18-19.

Applicants respectfully request withdrawal of the rejection.

V. Claims 4 and 5 Are Enabled

Claims 4 and 5 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing the enablement requirement. Office Action, pp. 8-9. While the Examiner acknowledges that the specification enables an "HBV core-like particle," the Examiner asserts that the specification does not enable an "HBV-like particle" (claim 4) and does not enable "HBV

precore protein as a therapeutic agent or a vaccine" (claim 5). *Id* at pg. 8. Applicants respectfully traverse.

Regarding claim 4, the Examiner bases the rejection on an alleged lack of description of the HBV-like particles. As set forth *supra*, however, the HBV core-like particles are described in the specification, namely through Figure 3 and supporting text. Moreover, the Examples in the specification provides guidance on how to obtain the claimed particles, including disclosing the amino acid sequence of the HBV precore protein that makes up the particle and fractionation procedures demonstrating existence of such particles from serum samples. Figure 1 and Examples 1 and 7.

Regarding claim 5, one skilled in the art would recognize the advantage of using virus-like particles as vaccines, as they lack the actual virus DNA and cannot infect other cells. Specific to hepatitis B, one skilled in the art would recognize that HBV core proteins are useful as vaccines. Schodel *et al.*, *Intervirology*, 39:104-110 (1996). Sakamoto, see *supra*, also teaches that sera from subjects infected with hepatitis B contain both particles that have cores and particles that lack cores. Sakamoto, abstract and Figures 1(a) and (d), which illustrate that the morphology of Dane particles and core particles are different. One skilled in the art, therefore, would recognize the ability of using virus-like particles to treat hepatitis B and that such particles can be obtained from sera. Correspondingly, since the claimed HBV precore protein and particles have been adequately described in the specification, as indicated *supra*, one skilled in the art would recognize the ability of the claimed particles to act as vaccines, as claimed.

In light of the arguments above, Applicants respectfully request the withdrawal of the rejection.

V. Claims 1, 2, 4-6 and 21 Are Not Anticipated

Claims 1, 2, 4-6 and 21 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Takahashi *et al.*, *J. Immunology* 147(9):3156-3160 (1991) ("Takahashi"). Office Action, pg. 10. Applicants respectfully traverse the rejection.

Takahashi describes an HBe antigen ($p20^e$) containing a precore sequence consisting of amino acids -29 to 149. Takahashi, abstract. However, an examination of Takahashi reveals no description that the $p20^e$ antigen is capable of forming particles as presently claimed. Moreover, as demonstrated by Figure 3(A) in Takahashi, the $p20^e$ antigen did not bind to antibodies raised against amino acids 19 to 29 of the precore-region product. *Id* at pg. 3158, left col. and Fig. 3(A). Because the claimed particle includes the HBV precore protein and would therefore bind to the antibodies above, it is a functionally distinct protein than the $p20^e$ protein. Accordingly, the $p20^e$ protein cannot be held as teaching the claimed HBV precore protein.

Furthermore, Figure 5 in the present specification illustrates that the HBV precore protein has a molecular weight that is greater than $p20^e$. Accordingly, the structures between the HBV precore protein and $p20^e$ are different, removing $p20^e$ as a product that teaches the claimed HBV precore protein.

Specifically regarding claim 2, the claim recites an "isolated HBV precore protein," wherein "the C-terminal is at positions 150-154." In start contrast, Takahashi suggests that the $p20^e$ protein does ***not*** contain amino acids 150-154 of the carboxyl-terminus because antibodies that bound to $p21^c$ did not bind to $p20^e$. Figure 3(C). Indeed, the previous Office Action acknowledges this fact. Office Action, pg. 10. The $p20^e$ particle, hence, is distinct from the claimed HBV precore protein in claim 2 that includes amino acids at positions 150-154.

Applicants respectfully request the withdrawal of the rejection.

VI. Claims 1-4 Are Not Obvious

Claims 1-4 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Takahashi, set forth *supra*, and Kobayashi *et al.*, *Gene* 30:227-232 (1984) ("Kobayashi"). The Examiner acknowledges that Takahashi fails to teach the claimed SEQ ID NO.: 1. Office Action, pp. 11-12. The Examiner, however, alleges that Kobayashi in combination with Takahashi render the instant claims obvious. *Id.* Applicants respectfully traverse the rejection.

Kobayashi describes an amino acid sequence comprising an HBV precore protein of adr strain. Kobayashi, abstract. According to the Office Action, this amino acid sequence is 99.6% identical to the claimed sequence. *Id.* While there is sequence similarity between the adr strain and the claimed HBV precore protein, one skilled in the art would not have found this teaching to obviate the instant claims.

As exemplified by the specification, the HBe antigen described by Takahashi differs from the claimed HBV precore protein by two amino acids sequences. Specification, Figure 1. However, this difference produces HBe in free form but not in particle form, whereas the opposite is true of the claimed HBV precore protein. *Id.* One skilled in the art would not have recognized that Kobayashi's teaching of an amino acid sequence that differs from the claimed sequence would have produced the claimed HBV precore protein, capable of forming virus-like particles. Specifically, there would be no reason for one skilled in the art to reasonably believe that a mutation at position 119, as indicated in the Office Action, would have produced a particle at all. Consequently, the obviousness rejection combining Takahashi and Kobayashi is improper.

Applicants respectfully request the withdrawal of the rejection.

VII. Conclusion

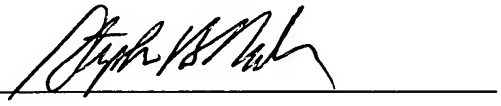
Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 14, 2008

By 

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